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ROD- AND CONE-MEDIATED VISUAL FUNCTION IN MULTIPLE SCLEROSIS

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SUMMARY

Visual thresholds and perceptual latencies were determined in patients with multiple sclerosis (MS) and in normal control subjects. Measurements were made under light- and dark-adapted conditions, with stimuli chosen to stimulate rod and cone receptors selectively. More abnormalities in perceptual latency and luminance threshold were recorded in the light-adapted condition than in the dark-adapted condition, but this result was not specific to the rod or cone systems. Possible underlying pathophysiological processes are discussed, and it is suggested that reduced conduction velocity in the demyelinated visual pathway is the most likely explanation of the observed perceptual delays and that there is no evident retinal contribution.

INTRODUCTION

Patients with multiple sclerosis (MS) or optic neuritis (ON) may have abnormally delayed visual conduction as judged either by the visual evoked response (VER) to pattern-reversal (Halliday et al. 1972) or by psychophysical tests of perceptual delay (Heron et al. 1974). This delay is less than 50 ms in most patients, but in some reaches 100 ms or more (Heron et al. 1974). Doubts were cast by these authors as to whether demyelination of the visual pathways alone can

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account for such large delays and it was suggested that there might be a contributory retinal component. In the normal visual system variations in response latency arise naturally, depending upon the adaptational state of the retina and on whether detection of the stimulus is mediated by rod or by cone receptors (Arden and Weale 1954; Roufs 1974; Lennie 1981). To investigate the possibility of a retinal component in MS, we have studied aspects of rod and cone function at various retinal sites in patients with MS and ON, and in normal control subjects. The variables measured included perceptual latency and luminance threshold, each evaluated under light- and dark-adapted conditions, with stimuli chosen to stimulate rods and cones selectively.

SUBJECTS

Six patients with MS and one with ON were studied. One eye was tested in each patient. The disease was classified according to the criteria of Rose et al. (1976). All but one patient had suffered previous symptoms in the eye tested, consistent with acute demyelination of the optic nerve; none had visual symptoms at the time of testing. Six patients had visual field defects shown by tangent screen examination (Patterson and Heron 1980); these consisted of arcuate scotomata between 10° and 25° eccentricity and were therefore outside the region of the visual field tested. Optic discs were all judged to be normal. Clinical details are given in Table 1.

As well as showing clinical evidence of demyelination in the eye tested, all patients selected had at least one abnormal retinal site, as indicated by an abnormal perceptual latency under light-adapted conditions (see below). Patients in whom such an abnormal site could not be demonstrated or in whom luminance threshold was excessively variable (Patterson et al. 1980) were excluded from this study. Approximately 50% of patients initially screened failed to meet the required criteria.

TABLE 1

CLINICAL DETAILS OF PATIENTS' EYES

Case number	Age (yr)	Sex	Diagnosis	Duration	Past visual symptoms	Acuity (Snellen)	Field defect
1	42	F	Probable MS	3 yr	+	6/5	+
2	29	F	Definite MS	4 mo	+	6/5	+
3	34	M	ON	2 mo	+	6/5	+
4	56	F	Definite MS	11 yr	−	6/6	+
5	27	M	Definite MS	4 yr	+	6/4	+
6	27	F	Probable MS	2 yr	+	6/5	−
7	31	F	Probable MS	2 yr	+	6/4	+

Seven healthy members of hospital staff acted as normal controls. The distribution of age, sex, and refractive error was similar in patient and control groups. The informed consent of all subjects was obtained after the nature of the procedure had been explained fully to them.

PROCEDURE

Subjects viewed a circular screen 0.6 m in diameter at a distance of 1.6 m, the angle of subtense being 21°. The eye not being tested was lightly occluded. An artificial pupil was not used. Spectacles or corrective lenses were worn if appropriate.

Stimulus flashes were supplied by two light-emitting diodes (LEDs), the intensities and timing of which were determined by suitable electronics. The angular subtense at the eye of each LED was 11 min arc. Flash intensity and onset asynchrony were controlled by the examiner, flash duration being fixed at 20 ms throughout (see Lennie 1981; Roufs 1974). (Spectral emission characteristics of the LEDs are summarized below.) One LED was placed at the centre of the screen and the other at 5° eccentricity. By rotation of the screen, 4 peripheral sites, at 45° to the horizontal meridian and 5° eccentricity in each quadrant, were examined.

For measurements of cone-mediated function, the white surface of the screen was illuminated by 4 incandescent lamps run from a regulated 250 V DC power supply. The resulting uniform, bright background field had luminance 3.0 log cd m^{-2} and colour temperature 2800 °K. Under these conditions, the rod system is known to saturate (Aguilar and Stiles 1954). The LEDs placed at the centre of the screen and at 5° eccentricity were red (MV5752) with peak-emission wavelength 630 nm.

For measurements of rod-mediated function, the screen was blackened and all background illumination was removed. The LED placed at the centre of the screen was red (as specified above) and the LED placed at 5° eccentricity was green (MV5252) with peak-emission wavelength 560 nm. A 1° square array of 4 miniature white lights surrounding the central LED was used to assist central fixation. The intensity of the array was adjusted so that it did not interfere with the adaptational state of the eye.

Luminance thresholds were determined by a method of limits (Engen 1971) and computed as the mean of two descending and ascending series with increments of 0.1 log units in intensity. Perceptual latency for each peripheral site relative to the fovea of the same eye was determined similarly with increments of 20 ms in onset asynchrony. Subjects were asked to say which light appeared first and to avoid making a judgement of simultaneity; the onset asynchrony was first set so that the foveal light was obviously leading and was then reduced until the peripheral light was judged to lead on two consecutive occasions. The peripheral light was then presented first and the onset asynchrony reduced until the foveal light appeared first on two consecutive occasions. This pair of runs was then repeated and the mean of the 4 values obtained was taken as the perceptual latency. For these latency measurements, stimulus intensities were set 0.5 log units above luminance

threshold on the selected background field. As a control on the selectivity of the stimuli for the rod and cone systems, threshold-recovery (dark-adaptation) curves were obtained at one peripheral site for each subject: after preliminary adaptation to approximately 4.2 log cd m^{-2} of white light, colour temperature 3000 °K, for 2 min, luminance threshold was determined at 1-min intervals with the green LED by a staircase method (Cornsweet 1962) on zero background field.

Patients were tested in 4 sessions of about 50 min each. In the first session, the light-adapted condition was used, and luminance threshold (cone increment threshold) was measured at the fovea and at a peripheral site. Perceptual latency relative to the fovea was then measured at that site. In the same way luminance threshold and perceptual latency were next measured at as many of the other 3 peripheral sites as possible before the subject fatigued. As a control, these measurements were repeated in the second session for the peripheral sites with the highest and lowest perceptual latencies. In the third session, a threshold-recovery curve was determined, usually at the site with the highest latency under light-adapted conditions. Luminance threshold (absolute rod threshold and absolute foveal cone threshold) and perceptual latency relative to the fovea were then determined under the dark-adapted condition at that site and at the other site tested in the second session. As a further control, these latency and threshold measurements were repeated in the fourth session after the subject had dark-adapted for 30 min.

Normal control subjects were tested similarly. Luminance thresholds and perceptual latencies were obtained at the 4 peripheral sites and a threshold-recovery curve was determined at one site for each subject.

RESULTS

From the results for normal eyes, means and standard deviations (SDs) were obtained for the following variables: asymptotic cone and rod thresholds as estimated from the threshold-recovery curves; and, by direct measurement, rod and cone thresholds and perceptual latencies for the foveal and peripheral sites for light- and dark-adapted conditions. In addition the normal ranges for inter-quadrant variation of perceptual latency at the peripheral sites were calculated for the two adaptation conditions. The normal range was taken to include 99% of a normal distribution. Data from patients were then expressed as normal or abnormal relative to these standard values. Table 2 summarizes results of the direct measurements (abnormal values indicated by [a]). [To allow easy comparison with previously published data, stimulus intensities are expressed here in photometric units, i.e. log μcd (photopic cd); for the green LED, 1 cd corresponds to 4.5 erg $\cdot$ s^{-1} $\cdot$ deg^{-2}, and, for the red LED, 1 cd corresponds to 16.8 erg $\cdot$ s^{-1} $\cdot$ deg^{-2}.]

Threshold-recovery curves and asymptotic thresholds

The general shape of the curves was similar in patients and controls, there being a clear rod-cone break at between 6 and 14 min. Representative examples are shown in Fig. 1. The value of threshold in the region of the rod-cone break

TABLE 2

RESULTS OF SITES TESTED IN PATIENTS' EYES

Field quadrants: SN superior nasal, ST superior temporal, IN inferior nasal, IT inferior temporal.

		Light-adapted			Dark-adapted		
		Threshold (log μcd)	Latency (ms)	Interquad latency (ms)	Threshold (log μcd)	Latency (ms)	Interquad latency (ms)
Normal limit	Fovea	max 2.4			max 1.4		
	Periphery	max 4.4	min −17 max 45	max 36	max 0.2	min 2 max 154	max 37
Case No.							
1	Fovea	3.3[a]	[a]		1.5[a]	[a]	
	SN	3.9	5[a]		−0.4	55[a]	
	IT	4.0	−80		−0.3	−5	
2	Fovea	3.1[a]			1.1		
	SN	4.3	65[a]		0	70	
	IT	4.0	10		−0.2	60	
3	Fovea	2.7[a]			1.1		
	SN	4.4	15		—	—	
	IN	4.5[a]	30[a]		−0.3	70	
	IT	4.4	−15		−0.3	50	
	ST	4.5[a]	5		—	—	
4	Fovea	3.3[a]			1.6[a]		
	SN	4.6[a]	40[a]		0.4[a]	90[a]	
	IN	4.5[a]	25		—	—	
	IT	4.6[a]	−10		−0.3	20	
5	Fovea	2.0			1.3		
	SN	3.9	15		—	—	
	IN	3.8	30[a]		−0.4	75[a]	
	IT	4.0	−10		−0.3	25	
6	Fovea	2.2			1.3		
	SN	4.4	50[a]		—	—	
	IN	4.3	75[a]		—	—	
	IT	4.0	80[a]		−0.2	140	
	ST	4.0	35		−0.4	110	
7	Fovea	2.1	[a]		1.4		
	SN	4.4	15[a]		—	—	
	IN	4.1	15[a]		−0.2	60[a]	
	IT	4.2	−45		−0.2	15	
	ST	4.2	10[a]		—	—	

[a] Outside normal range.

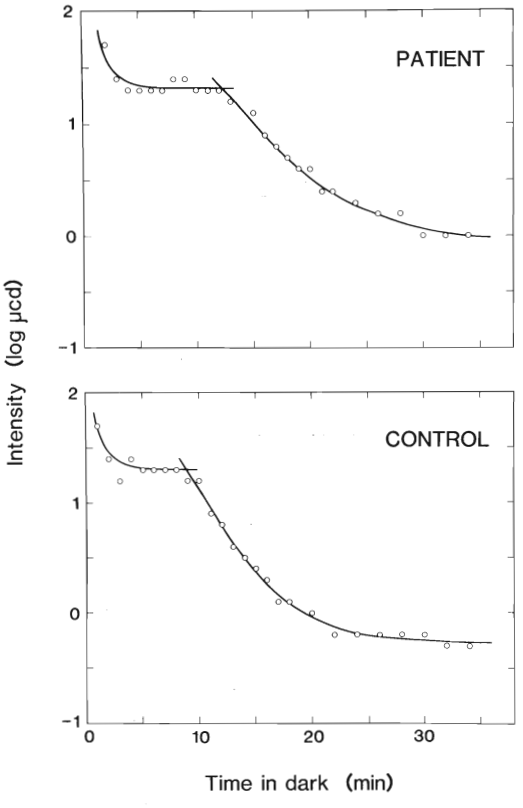

Fig. 1. Threshold-recovery curves for patient and normal control.

provided the only estimate of asymptotic (absolute) cone threshold. For absolute rod threshold, two estimates were available: one asymptotic value from the end section of the recovery curve, the other from direct measurements in the dark-adapted condition (see below). The difference in these two estimates of absolute rod threshold was small (about 0.15 log units on average).

For all subjects the difference between asymptotic cone threshold and absolute rod threshold (by direct measurement) was greater than 1 log unit. Setting flash intensity 0.5 log units above the appropriate luminance threshold in measuring perceptual latency (see Methods) was thus sufficient to secure isolation of the rod system in the dark-adapted condition. When data from the threshold-recovery curves for the patient and control groups were compared with a t-test, significant differences emerged: asymptotic cone threshold was raised in the patient group, $t = 2.78$, df = 12, $P < 0.05$, and difference in asymptotic cone threshold and absolute rod threshold was also raised, $t = 3.16$, df = 12, $P < 0.01$. However, comparison of absolute rod threshold in the two groups showed no significant difference, $t = 0.75$, df = 12, $P > 0.5$.

Foveal luminance threshold

This was abnormal in 4 patients for the light-adapted condition but in only 2 patients for the dark-adapted condition.

Foveal perceptual latency

This was classified abnormal if the latency of any peripheral site relative to the fovea of that eye was *less* than the normal range. Latency was thus abnormal in 2 patients for the light-adapted condition but in only 1 patient for the dark-adapted condition.

Peripheral luminance threshold

Five sites from 2 patients were abnormal when tested in the light-adapted condition; because experimental time was limited, only 3 of these sites could be tested in the dark-adapted condition, and only 1 was found to be abnormal. Repeatability of values at the same site in different sessions was similar in patients and controls.

Peripheral perceptual latency

Under the light-adapted condition, 1 site in each patient was abnormal by selection of the patient group. Four of these 7 sites were abnormal under the dark-adapted condition. Four other sites which were abnormal under the light-adapted condition were not tested in the dark-adapted condition because of patient fatigue. Repeatability of values at the same site in different sessions was similar in the 2 groups.

Rod-cone latency differences

The 7 preselected abnormal sites in the patients were compared as a group with the sites tested in the normal subjects for differences in rod and cone latencies. Although rod-cone latency differences were numerically smaller for the patient group (resulting mainly from increased cone latencies in the light-adapted condition) no significant difference between the 2 groups emerged ($t = 1.70$, $\mathrm{df} = 23$, $P > 0.1$).

DISCUSSION

Measurements made on patients at the foveal and peripheral sites are broadly similar in that more abnormalities of luminance threshold and perceptual latency are found under the light-adapted condition than under the dark-adapted condition. Since the foveal site (11 min arc angular subtense) was rod-free, it seems likely that these differences result not from some specificity of the disease for the cone system, but from the effects of background luminance itself. In MS patients, luminance threshold may be normal at low background luminance levels but raised abnormally at high background levels, as used in this study, although the most striking effect is to cause an increase in the variability of luminance threshold (Patterson et al. 1980). Luminance threshold was not excessively variable for the

patients in this series, partly because the patients were selected for their relatively stable thresholds and also because our method of measurement (method of limits) is less sensitive to threshold fluctuations than the randomized-block technique used in the previous study (Patterson et al. 1980) to obtain frequency-of-seeing curves. Patterson et al. (1980) have discussed some of the possible pathophysiological processes that might produce an abnormal dependence of luminance threshold on the level of background luminance, but why perceptual latency might be similarly vulnerable is less easy to interpret.

The fact that the threshold-recovery curves show a significant increase in asymptotic cone threshold but not in absolute rod threshold for the patient group might suggest a preferential effect of demyelination for cone pathways. It should be noted, however, that the legitimacy of extrapolating the first section of the threshold-recovery curve to estimate asymptotic cone threshold may be uncertain for MS patients; if the attainment of maximum cone sensitivity were abnormally delayed in patients, the rod-cone break might occur before absolute cone threshold was reached, resulting in a spuriously high estimate. There is indeed evidence that in some patients with optic neuritis sensitivity is diminished transiently following exposure to intense illumination (Sunga and Enoch 1970).

Overall then we find no unequivocal evidence for a differential effect of MS on rod or cone systems. This result of course does not preclude a retinal effect in which both systems are equally affected. If, at the abnormal site, any disease process introducing an additional delay were to affect rod and cone systems equally, then by subtracting contributions to rod and cone latencies for that site, one should obtain a quantity indistinguishable from that for a normal site, which may have been the case here.

A retinal component was first suggested as a contributory factor to explain markedly delayed VERs to pattern-reversal (Halliday et al. 1972) and also abnormal perceptual latencies of up to 110 ms, as measured psychophysically (Heron et al. 1974), it being argued that such delays might not be explained solely by reduction of conduction velocity in the demyelinated visual pathway. Experiments on demyelinated nerve fibre in rat (Bostock and Sears 1976) have since shown that conduction may be maintained over demyelinated segments as long as 500 μm, conduction velocities being reduced to one-twentieth of normal. If these results were to hold for the demyelinated pathway of man, then a simple calculation shows that to account for the observed psychophysical delays it would be necessary to have about 5 cm of demyelinating lesion. This 5 cm could be discontinuous, and, since both anterior and posterior visual pathways may be demyelinated in MS (Savitsky and Rangell 1950), it seems possible that such a *total* length might occur in the 15 cm or so between lamina cribrosa and visual cortex. But, as McDonald (1977) has pointed out, there are limitations in extrapolating data from the peripheral nervous system in animals to the central nervous system in man.

Studies of the electroretinogram (ERG) in MS patients have failed to provide unambiguous evidence of retinal involvement. Gills (1966) found a decreased *b* wave amplitude in patients with advanced MS, and similar results were obtained

by Ikeda et al. (1978) who stressed that diminished ERG amplitude was found in eyes which also showed diminished amplitude of the VER to pattern reversal. But, in a study of eyes with acute optic neuritis by Halliday et al. (1972), all ERGs were observed to be normal. Electroretinograms with subnormal, normal, or enhanced *b* wave amplitudes were recorded by Feinsod et al. (1973), the amplitude bearing no relation to either the severity of symptoms or the duration of disease. Abnormal latency of the *b* wave is not reported in any of these studies and since the *b* wave reflects bipolar cell function, any putative increased retinal delay would have to occur subsequent to the bipolar-cell layer.

In summary, there is little positive evidence for a retinal contribution to the observed perceptual and VER delays in MS, and in the present state of knowledge it seems that these are explained most readily by reduced conduction velocity in the demyelinated visual pathway.

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